

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**21-061/SE2-007**

**21-062/SE2-008**

**STATISTICAL REVIEW(S)**

## **STATISTICAL REVIEW AND EVALUATION**

**NDA#:** 21-061 S-007 and 21-062 S-008

**Name of Drug:** TEQUIN™ Tablets (gatifloxacin) and  
TEQUIN™ I.V. (gatifloxacin)

**Applicant:** Bristol-Myers Squibb Company

**Indications:** Acute exacerbation of chronic bronchitis

**Documents Reviewed:** Volumes 1, 2, 4, 5, and 6 and electronic submission dated  
December 21, 2000; and amendments dated 3/7/01, 3/28/01,  
4/18/01, 5/24/01, 6/1/01, and 6/26/01

**Review Type:** Clinical data

**Statistical Reviewer:** Nancy Silliman, Ph.D., SGE

**Medical Officer:** Rosemary Johann-Liang, MD, HFD-590

**Project Manager:** Diana Willard, HFD-590

**Keywords:** quinolone, fluoroquinolone, dynamic randomization

### **TABLE OF CONTENTS**

<b><u>I. INTRODUCTION</u></b> .....	2
<b><u>II. CONTROLLED CLINICAL STUDIES 064 AND 065</u></b> .....	2
<b><u>1. Study Objectives and Design</u></b> .....	2
<b><u>2. Efficacy Results</u></b> .....	5
<b><u>2.1. Study Population</u></b> .....	5
<b><u>2.1.a. Study 064</u></b> .....	5
<b><u>2.1.b. Study 065</u></b> .....	6
<b><u>2.2. Primary Efficacy Results, Clinically Evaluable Patients</u></b> .....	8
<b><u>2.2.a. Study 064</u></b> .....	8
<b><u>2.2.b. Study 065</u></b> .....	9
<b><u>2.3. Primary Efficacy Results, Eligible Patients</u></b> .....	9
<b><u>2.3.a. Study 064</u></b> .....	9
<b><u>2.3.b. Study 065</u></b> .....	10
<b><u>2.4. Secondary Efficacy Results</u></b> .....	10
<b><u>2.4.a. Study 064</u></b> .....	10
<b><u>2.4.b. Study 065</u></b> .....	15
<b><u>3. Safety</u></b> .....	18
<b><u>3.1. Study 064</u></b> .....	18
<b><u>3.2. Study 065</u></b> .....	20
<b><u>III. CONCLUSIONS</u></b> .....	23

## I. INTRODUCTION

Oral and intravenous formulations of gatifloxacin (Tequin®) were approved on December 17, 1999 for the treatment of acute exacerbation of chronic bronchitis (AECB), among other indications. The currently labeled treatment course of gatifloxacin for AECB is 400 mg once daily for 7-10 days. In this supplemental New Drug Application, the sponsor has submitted two controlled clinical trials, studies AI420-064 and AI420-065 (hereafter referred to as studies 064 and 065, respectively) to support reducing the duration of treatment for AECB to 5 days. Study 064 compares a 5-day course of oral gatifloxacin, given 400mg QD, to both a 7-day course of oral gatifloxacin given 400mg QD and a 10-day course of oral clarithromycin given 500mg BID. Study 065 compares a 5-day course of oral gatifloxacin given 400mg QD to a standard regimen of azithromycin (500 mg PO on day 1, followed by 250 mg PO on days 2-5). In both studies, efficacy and safety results were similar between treatment arms.

## II. CONTROLLED CLINICAL STUDIES 064 AND 065

### **1. Study Objectives and Design**

Studies 064 and 065 were both randomized, double-blind, double-dummy, multi-center studies comparing a 5-day course of oral gatifloxacin given 400mg QD to approved therapies for the treatment of AECB. In study 064 there were two comparators: a 7-day course of oral gatifloxacin given 400mg QD and a 10 day course of oral clarithromycin given 500mg BID. In study 065, the comparator was a standard regimen of azithromycin (500 mg PO on day 1, followed by 250 mg PO on days 2-5). Randomization was stratified by usage of inhaled or systemic steroids. Study 064 was conducted between November 1998 and July 1999, and enrolled 532 patients at 35 centers in the United States. Two of these investigators, Dr. C. Andrew DeAbate (investigator #023) and Dr. C.P. Mathew (investigator #024), have received Notice of Initiation of Disqualification Proceedings and Opportunity to Explain Letters from the Food and Drug Administration, dated April 13, 2001 and June 27, 2001, respectively. These letters allege, among other things, that both investigators submitted false information to the sponsor and FDA by altering patient records and creating patients who do not appear to exist or who are not unique. As a result, this review will present the primary results of study 064 in two ways: (1) including all patients allegedly randomized to study treatment, and (2) excluding those patients from both Dr. DeAbate's center (97 patients) and his sub-investigator, — (100 patients). Note that together, Drs. DeAbate and — enrolled 37% of the patients in study 064. Study 065 was conducted between October 1999 and May 2000, and enrolled 296 patients at 33 centers in the United States.

The primary objective of each study was to demonstrate that a 5-day course of gatifloxacin achieves an efficacy rate similar to that of an approved comparator. *In the original protocol for study 064, the comparison between the 5-day gatifloxacin regimen and the clarithromycin regimen was deemed the sole primary objective. Other treatment comparisons (i.e., between the two gatifloxacin regimens and between the 7-day gatifloxacin and clarithromycin regimens) were considered secondary objectives. As a result, no adjustments to the Type I error for multiple treatment comparisons are necessary in the analysis. Ninety-five percent confidence intervals are used for all treatment comparisons in study 064; the "success" or "failure" of study 064 depends only on the primary comparison. Secondary objectives included documenting bacteriologic efficacy, assessing safety of all treatment regimens, and comparing time to improvement and resolution of cardinal symptoms (study 065 only). Study 065 also followed*

patients who were cured clinically for 6 months after their last dose of study medication. The two objectives of this extended phase of the study were to assess the impact of gatifloxacin and azithromycin treatment on carriage and resistance of nasopharyngeal flora, and to compare the time to the next occurrence of AECB. *The extended phase of study 065 will not be addressed in this review.*

Eligible patients were those who had a clinical diagnosis of chronic bronchitis, i.e., having a chronic cough and sputum production on most days for 3 consecutive months for at least 2 consecutive years. Clinical and bacteriologic responses to study therapy were to be assessed at the Test of Cure (TOC) visit (Day +7 to +14 post-treatment; study analysis plans were amended to include data from Day +5 to Day +18). Among patients with a clinical response of cured at the TOC visit, relapse was evaluated at the Extended Follow-up visit (Day +21 to Day +28). A patient was considered to have relapsed if they received alternative antibiotic therapy due to signs and symptoms of an acute bronchial infection. In study 065, patients were also considered to have relapsed if symptoms related to AECB returned after the initial resolution/improvement, or if new clinical symptoms of acute bronchial infection appeared without documentation of a new pathogen.

Clinical response was defined as follows (taken from the sponsor's Final Study Report for Study 065, Section 5.8.6.3.1):

- **CURED**: All signs and symptoms related to the acute infection (cough, dyspnea, sputum production, and sputum purulence) have improved or returned to the patient's baseline level with the original therapy alone and without need for further antimicrobials. In addition, no new signs or symptoms of acute infection were present; and if elevated at study entry, fever was resolved (i.e., temperature  $\leq 38^{\circ}\text{C}$  or  $100.4^{\circ}\text{F}$ ) (Note: Baseline is defined as the patient's assessment of their typical/usual condition when free of acute infection).
- **FAILURE**:
  - New clinical signs and symptoms of acute infection appeared, or
  - If present at study entry, the patient still has fever (i.e., temperature  $>38^{\circ}\text{C}$  or  $100.4^{\circ}\text{F}$ ), or
  - Clinical/radiological evidence of pneumonia; or
  - Another antibiotic was required for treatment of this acute episode despite the resolution or improvement of signs and symptoms; or
  - One or more signs and symptoms of acute infection have failed to improve.
- **UNABLE TO DETERMINE**: No follow-up beyond the pre-treatment visit.

Bacteriologic response was defined as follows (taken from the sponsor's Final Study Report for Study 065, Section 5.8.6.3.2):

- **ERADICATED**
  - **Documented Eradicated**: The original pathogen was absent in the culture of a good quality (i.e.,  $> 25$  PMN per LPF) sputum specimen.
  - **Presumed Eradicated**: The subject was not producing sputum (i.e., there was no source to culture) or no sputum was obtained, and the Clinical Response is Cured.

- **PERSISTED**

- **Documented Persisted:** The original pathogen was present in the culture of a good quality (i.e., > 25 PMN per LPF) sputum specimen.
- **Presumed Persisted:** The subject was not producing sputum (i.e., there was no source to culture) or no sputum was obtained, and the Clinical Response is Failure.

- **UNABLE TO DETERMINE**

- The clinical response of the patient in question was designated Unable to Determine.

There were four populations of interest: all treated patients, eligible patients, clinically evaluable patients, and microbiologically evaluable patients. All treated patients were those who received at least one dose of study drug. Eligible patients also had to have a diagnosis of AECB at study entry. Clinically evaluable patients were eligible patients who received at least 8 days (study 064) or 4 days (study 065) of study drug (at least 3 days for failures), had a TOC assessment, and received no systemic antibacterial with documented activity against the most common respiratory pathogens for an infection other than a lower respiratory tract infection prior to TOC. Microbiologically evaluable patients were clinically evaluable patients with at least one pathogen that was susceptible to all study medications.

The sponsor's primary efficacy assessment was based on the analysis of clinical response in clinically evaluable patients. *As the analysis in clinically evaluable patients is susceptible to bias (patients can be excluded based on post-randomization characteristics), this reviewer considers clinical response in eligible patients to be equally important.* As established in the original protocol and agreed to by FDA, similarity between the 5 day gatifloxacin and comparator regimens is considered established if the lower bound of a 95% confidence interval around the difference in clinical cure rates, gatifloxacin minus comparator, is greater than or equal to -15%. *Note that the Division of Special Pathogens and Immunologic Drug Products is considering establishing smaller deltas for many of the respiratory indications. In the future, a delta of 10% or smaller may be required in trials such as these.*

The sponsor used a modification of the Fleiss method (Fleiss, J.L. Statistical Methods for Rates and Proportions, Second Edition, pgs. 161-165, New York: John Wiley & Sons, 1981) to calculate confidence intervals which account for possible heterogeneity of response by the stratification factor, systemic/inhaled corticosteroid use at randomization.

Although the Fleiss method was not mentioned in either original protocol, it is mentioned in the final analysis plans which were approved prior to locking of the final databases. The final analysis plans state that "a SAS macro, developed by the BMS Biostatistics and Data Management Department, will be used to calculate this adjusted confidence interval."

The original Fleiss method calculates adjusted confidence limits using a weighted average of the simple stratum-specific rate differences, where the inverse of the variance of the estimated rate difference within the stratum is used as the weight for the corresponding stratum.

where the n's correspond to the number of patients on each treatment in stratum i. Incorporating a continuity correction at this stage (when calculating stratum-specific rate differences) has the effect of shifting the entire confidence interval to the left. The standard continuity correction that is used for an unadjusted confidence interval around a difference in rates widens the confidence interval by shifting the lower limit to the left and the

upper limit to the right. However, both methods shift the lower limit to the left, and it is the lower limit that we are interested in here. Confidence limits using both the original Fleiss method and the BMS modification will be presented in this review.

At the time of randomization, patients were stratified based on current inhaled/systemic steroid use. In study 064, the randomization system used a dynamic balancing algorithm which adjusted the randomization probabilities in order to minimize any imbalance of treatment arms within each center, within each steroid use group, and for the overall study (reference: Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975; 31:103-115). When a new patient was presented for randomization into the study, the algorithm calculated the value of an imbalance function given randomization into each of the treatment arms. The imbalance function was the sum of the largest difference between treatment arms within each strata and overall. The treatment assignment that would result in the least imbalance was then assigned with a probability that was a function of the maximum potential imbalance that could occur. *This choice of randomization complicates the interpretation of results for study 064, as there is currently no known way to account for the dynamic randomization in the analysis of data from an active-controlled trial with binary outcome data. Analysis presented here assumes simple randomization, and it is unknown whether such analysis is too conservative or too liberal. As part of ongoing discussions between statisticians at the FDA and Bristol-Myers Squibb (BMS) during the drug development process for gatifloxacin, BMS performed various simulations in an attempt to address this issue. Although only a finite number of models could be investigated, these simulations suggest that the results found in these studies are unlikely to be too liberal. However, this result has not been proven theoretically.* In study 065, the randomization system used a permuted block design that allocated blocks of four to each stratum within a site.

## 2. Efficacy Results

### 2.1. Study Population

#### 2.1.a. Study 064

In study 064, a total of 532 patients were enrolled at 35 sites. Excluding investigators DeAbate and Mathew, a total of 335 patients were randomized at 33 sites. Five patients never received study drug (1 5-day gatifloxacin patient, 1 7-day gatifloxacin patient, and 3 clarithromycin patients). Of the 527 patients treated, 54% were male, 61% were white, and the median age was 45 years old. Approximately 8% of patients in each treatment arm were using systemic corticosteroids at the time of randomization. Baseline characteristics were generally similar among treatment groups, with the exception of background asthma rates which were somewhat lower in the 5-day gatifloxacin group. Including all treated patients, 32 (18%) 5-day gatifloxacin patients, 45 (26%) 7-day gatifloxacin patients, and 42 (24%) clarithromycin patients had asthma at the time of randomization. The difference was somewhat more noticeable when patients enrolled by Drs. DeAbate and Mathew were excluded: 21 (19%) 5-day gatifloxacin patients, 38 (34%) 7-day gatifloxacin patients, and 29 (27%) clarithromycin patients. Approximately 90% of patients in each treatment arms received the full 10 days of study therapy. Two percent of 5-day gatifloxacin patients, 5% of 7-day gatifloxacin patients, and 3% of clarithromycin patients discontinued study drug. The majority of patients in each treatment arm who discontinued study drug discontinued due to an adverse event.

Table 2.1.a summarizes the distribution of patients in the different study populations and reasons for exclusion from those study populations. Of the all treated patients, 106 (61%) 5-day gatifloxacin patients, 99 (57%) 7-day gatifloxacin patients, and 105 (59%) clarithromycin patients had pathogens. Seventy (40%) 5-day gatifloxacin patients, 65 (37%) 7-day gatifloxacin patients, and 76 (43%) clarithromycin patients were considered microbiologically evaluable. Reasons for exclusion from the study populations were similar among treatment groups. Results excluding investigators DeAbate and Mathew are similar to those shown below.

**Table 2.1.a. Distribution of Patients in Study Populations and Reasons for Exclusion, All Treated Patients (Study 064 – All Patients)**

	Number of Patients (%)			
	Gatifloxacin 5-Day N = 174	Gatifloxacin 7-Day N = 175	Clarithromycin 10-Day N = 178	Total N = 527
<b>Eligible</b>	170 (98)	171 (98)	174 (98)	515 (98)
<b>Ineligible</b>	4 (2)	4 (2)	4 (2)	12 (2)
<u>Reason Ineligible:</u>				
No pre-treatment purulent sputum specimen	3 (2)	3 (2)	2 (1)	8 (2)
Chest x-ray outside window	--	1 (< 1)	2 (1)	3 (< 1)
Did not have chronic bronchitis	1 (< 1)	--	--	1 (< 1)
<b>Clinically Evaluable</b>	151 (87)	154 (88)	163 (92)	468 (89)
<b>Clinically Unevaluable</b>	23 (13)	21 (12)	15 (8)	59 (11)
<u>Reason Unevaluable:</u>				
No Test of Cure Visit	16 (9)	11 (6)	9 (5)	36 (7)
Ineligible	4 (2)	4 (2)	4 (2)	12 (2)
Insufficient dosage	2 (1)	5 (3)	2 (1)	9 (2)
Other antibiotic received	1 (< 1)	1 (< 1)	--	2 (< 1)

#### *2.1.b. Study 065*

In study 065, a total of 296 patients were enrolled at 33 sites. Two azithromycin patients never received study drug. Of the 294 patients treated, 53% were female, 80% were white, and the median age was 52 years old. Approximately 30% of patients in each treatment arm were using systemic corticosteroids at the time of randomization. Baseline characteristics were generally similar among treatment groups. A little more than 90% of patients in each treatment arm (93% gatifloxacin, 91% azithromycin) received the full 5 days of study therapy. Two percent of gatifloxacin patients and 5% of azithromycin patients discontinued study drug. The majority of patients in each treatment arm who discontinued study drug discontinued due to an adverse event.

Table 2.1.b summarizes the distribution of patients in the different study populations and reasons for exclusion from those study populations. Of the all treated patients, 104 (71%) gatifloxacin patients and 102 (69%) azithromycin patients had pathogens. Seventy-three (50%) gatifloxacin

patients and 74 (50%) azithromycin patients were considered microbiologically evaluable. Reasons for exclusion from the study populations were similar among treatment groups.

**Table 2.1.b. Distribution of Patients in Study Populations and Reasons for Exclusion, All Treated Patients (Study 065)**

Reason	Number of Patients (%)		
	Gatifloxacin N = 147	Azithromycin N = 147	Total N = 294
<b>Eligible</b>	142 (97)	138 (94)	280 (95)
<b>Ineligible</b>	5 (3)	9 (6)	14 (5)
<u>Reason ineligible:</u>			
Did not have required symptoms at entry	--	5 (3)	5 (2)
No pre-treatment purulent sputum specimen	3 (2)	1 (< 1)	4 (1)
Evidence of pneumonia on pre-treatment x-ray	1 (< 1)	2 (1)	3 (1)
Possibly treated in previous gatifloxacin trial	1 (< 1)	--	1 (< 1)
Consent not obtained in window	--	1 (< 1)	1 (< 1)
<b>Clinically Evaluable</b>	127 (86)	125 (85)	252 (86)
<b>Clinically Unevaluable</b>	20 (14)	22 (15)	42 (14)
<u>Reason unevaluable:</u>			
Ineligible	5 (3)	9 (6)	14 (5)
Post-treatment evaluation out of window or done via phone	7 (5)	6 (4)	13 (4)
Insufficient dosage	2 (1)	5 (3)	7 (2)
No post-treatment evaluation	2 (1)	2 (1)	4 (1)
Lost to follow-up	3 (2)	--	3 (1)
Other antibiotic received	1 (< 1)	--	1 (< 1)

## 2.2. Primary Efficacy Results, Clinically Evaluable Patients

### 2.2.a. Study 064

Table 2.2.a.1 summarizes clinical response rates for all clinically evaluable patients. Table 2.2.a.2 summarizes clinical response rates for clinically evaluable patients, excluding those enrolled by Drs. DeAbate and Mathew. Cure rates were considered similar between the 5-day gatifloxacin and clarithromycin arms. Using the acceptable difference limit of 15%, results are fairly robust and conclusions are not likely to be affected by the dynamic randomization used in this study. *Note that these results also satisfy a delta of 10%.*

**Table 2.2.a.1. Clinical Response, Clinically Evaluable Patients  
(Study 064 – All Patients)**

	Number of Patients (%)			Total N = 468
	Gatifloxacin 5-Day N = 151	Gatifloxacin 7-Day N = 154	Clarithromycin 10-Day N = 163	
Cure	135 (89)	136 (88)	145 (89)	416 (89)
Failure	16 (11)	18 (12)	18 (11)	52 (11)

95% Confidence Interval for Difference in Cure Rates (Fleiss method):

5-day gatifloxacin vs. 10-day clarithromycin, primary comparison: (-5.1%, 7.9%).

95% Confidence Intervals for Difference in Cure Rates (BMS modification of Fleiss method):

5-day gatifloxacin vs. 10-day clarithromycin, primary comparison: (-6.1%, 7.0%);

5-day gatifloxacin vs. 7-day gatifloxacin: (-5.5%, 8.0%); and

and 7-day gatifloxacin vs. 10-day clarithromycin (-8.9%, 5.0%).

**Table 2.2.a.2. Clinical Response, Clinically Evaluable Patients  
(Study 064 – Excluding Patients Enrolled by Drs. DeAbate and Mathew)**

	Number of Patients (%)			Total N = 300
	Gatifloxacin 5-Day N = 97	Gatifloxacin 7-Day N = 102	Clarithromycin 10-Day N = 101	
Cure	86 (89)	86 (84)	86 (85)	258 (86)
Failure	11 (11)	16 (16)	15 (15)	42 (14)

95% Confidence Interval for Difference in Cure Rates (Fleiss method):

5-day gatifloxacin vs. 10-day clarithromycin, primary comparison: (-3.7%, 13.9%).

95% Confidence Intervals for Difference in Cure Rates (BMS modification of Fleiss method):

5-day gatifloxacin vs. 10-day clarithromycin, primary comparison: (-5.3%, 12.3%);

5-day gatifloxacin vs. 7-day gatifloxacin: (-4.4%, 13.6%); and

and 7-day gatifloxacin vs. 10-day clarithromycin (-12.7%, 6.9%).

### 2.2.b. Study 065

Table 2.2.b summarizes clinical response rates for all clinically evaluable patients. Cure rates were considered similar between the 5-day gatifloxacin and azithromycin arms using the 15% delta. *Note that these results also satisfy a delta of 10%.*

**Table 2.2.b. Clinical Response, Clinically Evaluable Patients (Study 065)**

Clinical Response	Number of Patients (%)		Total N = 252
	Gatifloxacin N = 127	Azithromycin N = 125	
Cure	104 (82)	92 (74)	196 (78)
Failure	23 (18)	33 (26)	56 (22)

95% Confidence Interval for Difference in Cure Rates (Fleiss method): (-1.8%, 18.6%).

95% Confidence Interval for Difference in Cure Rates (BMS Modification of Fleiss method): (-3.4%, 17.0%).

### 2.3. Primary Efficacy Results, Eligible Patients

#### 2.3.a. Study 064

Table 2.3.a.1 summarizes clinical response rates for all eligible patients. Table 2.3.a.2 summarizes clinical response rates for eligible patients, excluding those enrolled by Drs. DeAbate and Mathew. Cure rates were considered similar between the 5-day gatifloxacin and clarithromycin arms. Using the acceptable difference limit of 15%, results are fairly robust and conclusions are not likely to be affected by the dynamic randomization used in this study. *Note that these results also satisfy a delta of 10%.*

**Table 2.3.a.1. Clinical Response, Eligible Patients  
(Study 064 – All Patients)**

Clinical Response	Number of Patients (%)			Total N = 515
	Gatifloxacin 5-Day N = 170	Gatifloxacin 7-Day N = 171	Clarithromycin 10-Day N = 174	
Cure	147 (86)	147 (86)	151 (87)	445 (86)
Failure	18 (11)	21 (12)	19 (11)	58 (11)
Unable to Determine	5 (3)	3 (2)	4 (2)	12 (2)

95% Confidence Interval for Difference in Cure Rates (Fleiss method):

5-day gatifloxacin vs. 10-day clarithromycin, primary comparison: (-6.7%, 7.3%).

95% Confidence Intervals for Difference in Cure Rates (BMS modification of Fleiss method):

5-day gatifloxacin vs. 10-day clarithromycin, primary comparison = (-7.7%, 6.4%);

5-day gatifloxacin vs. 7-day gatifloxacin = (-6.9%, 7.5%);

7-day gatifloxacin vs. 10-day clarithromycin = (-9.2%, 5.2%).

**Table 2.3.a.2. Clinical Response, Eligible Patients**  
(Study 064 – Excluding Patients Enrolled by Drs. DeAbate and Mathew)

Clinical Response	Number of Patients (%)			Total N = 318
	Gatifloxacin 5-Day N = 105	Gatifloxacin 7-Day N = 109	Clarithromycin 10-Day N = 104	
Cure	92 (88)	92 (84)	88 (85)	272 (86)
Failure	13 (12)	17 (16)	16 (15)	46 (14)

95% Confidence Interval for Difference in Cure Rates (Fleiss method):

5-day gatifloxacin vs. 10-day clarithromycin, primary comparison: (-4.8%, 13.1%).

95% Confidence Intervals for Difference in Cure Rates (BMS modification of Fleiss method):

5-day gatifloxacin vs. 10-day clarithromycin, primary comparison = (-6.3%, 11.6%);

5-day gatifloxacin vs. 7-day gatifloxacin = (-5.7%, 12.1%);

7-day gatifloxacin vs. 10-day clarithromycin = (-11.9%, 7.5%).

#### 2.3.b. Study 065

Table 2.3.b summarizes clinical response rates for all eligible patients. Cure rates were considered similar between the 5-day gatifloxacin and azithromycin arms using a 15% delta.

*Note that these results also satisfy a delta of 10%.*

**Table 2.3.b. Clinical Response, Eligible Patients (Study 065)**

Clinical Response	Number of Patients (%)		Total N = 280
	Gatifloxacin N = 142	Azithromycin N = 138	
Cure	110 (77)	98 (71)	208 (74)
Failure	27 (19)	37 (27)	64 (23)
Unable to Determine	5 (4)	3 (2)	8 (3)

95% Confidence Interval for Difference in Cure Rates (Fleiss method): (-3.8%, 16.7%).

95% Confidence Interval for Difference in Cure Rates (BMS Modification of Fleiss method): (-5.2%, 15.3%).

#### 2.4. Secondary Efficacy Results

##### 2.4.a. Study 064

Table 2.4.a.1 summarizes clinical cure rates by prognostic factor for clinically evaluable patients. Results were similar when patients enrolled by Drs. DeAbate and Mathew were excluded. In both populations, cure rates in each treatment arm tended to be lower for those patients using systemic corticosteroids at the time of randomization, and higher for current smokers. *Note that while the same difference in cure rates by smoking status was seen for gatifloxacin in the two controlled bronchitis studies submitted with the original NDA (studies AI420-001 and AI420-020), it was not duplicated in either the unblinded study submitted with the original NDA (study AI420-004) or study 065. As in the original NDA submission, it appears that most of the difference in this study can be explained by noting that non-smokers are at a higher risk for failure based on other prognostic factors. For example, a larger percentage of non-smokers were older than 65, had a history of asthma, and were using steroids at the time of randomization.*

**Table 2.4.a.1. Clinical Cure Rates by Prognostic Factor, Clinically Evaluable Patients  
(Study 064 – All Patients)**

Prognostic Factor/ Subcategory	Number Cured/Evaluable Patients (%)			
	Gatifloxacin 5-day N = 151	Gatifloxacin 7-Day N = 154	Clarithromycin 10-Day N = 163	Total N = 468
<u>Exacerbation type</u>				
Type I	111/124 (90)	110/127 (87)	118/136 (87)	339/387 (88)
Type II	23/26 (88)	26/27 (96)	27/27 (100)	76/80 (95)
Type III	1/1 (100)	--	--	1/1 (100)
<u>Duration of current episode</u>				
0 - 7 Days	86/101 (85)	98/110 (89)	102/109 (94)	286/320 (89)
> 7 Days	48/49 (98)	36/40 (90)	43/54 (80)	127/143 (89)
Not recorded	1/1 (100)	2/4 (50)	--	3/5 (60)
<u>Pre-treatment systemic corticosteroid use</u>				
Yes	9/14 (64)	10/12 (83)	11/14 (79)	30/40 (75)
No	126/137 (92)	126/142 (89)	134/149 (90)	386/428 (90)
<u>Current smoking status</u>				
Smoker	94/101 (93)	94/99 (95)	97/107 (91)	285/307 (93)
Non-smoker	41/50 (82)	42/55 (76)	48/56 (86)	131/161 (81)
<u>History of smoking</u>				
Yes	120/134 (90)	123/137 (90)	130/144 (90)	373/415 (90)
No	15/17 (88)	13/17 (76)	15/19 (79)	43/53 (81)

**APPEARS THIS WAY  
ON ORIGINAL**

Table 2.4.a.2 summarizes clinical response at the extended follow-up visit for clinically evaluable patients. Results were similar among treatment groups. Results also changed very little when patients enrolled by Drs. DeAbate and Mathew were excluded. As outlined in the sponsor's analysis plan, the end of study cure rates are calculated by carrying forward TOC values for those patients with no data at the extended follow-up visit (i.e., cures are carried forward from the TOC visit to the end of study evaluation). If one instead assumes that patients who were lost to follow-up by the end of study are failures, the end of study cure rates are 85% (129/151) for 5-day gatifloxacin patients, 87% (134/154) for 7-day gatifloxacin patients, and 87% (142/163) for clarithromycin patients.

**Table 2.4.a.2. Clinical Assessment at Extended Follow-up, Clinically Evaluable Patients  
(Study 064 – All Patients)**

	Numbers of Patients (%)			
	Gatifloxacin 5-Day N = 151	Gatifloxacin 7-Day N = 154	Clarithromycin 10-Day N = 163	Total N = 468
Cured at Test of Cure Visit	135 (89)	136 (88)	145 (89)	416 (89)
Extended Follow-Up obtained	131 (97)	136 (100)	145 (100)	412 (99)
Sustained cure	129 (98)	134 (99)	142 (98)	405 (98)
Relapse	2 (2)	2 (1)	3 (2)	7 (2)
Cure rate at end of study <sup>a</sup>	133/151 (88)	134/154 (87)	142/163 (87)	409/468 (87)

<sup>a</sup> 95% Confidence Intervals for Difference in Cure Rates  
(Normal Approximation to the Binomial Distribution Incorporating a Continuity Correction):  
5-day gatifloxacin vs. 10-day clarithromycin = (-7.0%, 8.9%);  
5-day gatifloxacin vs. 7-day gatifloxacin = (-7.0%, 9.1%);  
7-day gatifloxacin vs. 10-day clarithromycin = (-8.1%, 7.9%).

Table 2.4.a.3 summarizes bacteriologic eradication rates for the major pathogens in all microbiologically evaluable patients. Table 2.4.a.4 summarizes the same information excluding patients enrolled by Drs. DeAbate and Mathew. Note that overall numbers of pathogens are considerably diminished when patients enrolled by Drs. DeAbate and Mathew are excluded.

**APPEARS THIS WAY  
ON ORIGINAL**

**Table 2.4.a.3. Bacteriologic Eradication Rates for the Major Pathogens,  
Microbiologically Evaluable Patients  
(Study 064 – All Patients)**

Pathogen <sup>a</sup>	Number Eradicated/No. Isolated (%)			
	Gatifloxacin 5-Day	Gatifloxacin 7-Day	Clarithromycin 10-Day	Total
Total	85/87 (98)	75/80 (94)	87/89 (98)	247/256 (96)
<i>H. influenzae</i>	15/15 (100)	21/22 (95)	18/18 (100)	54/55 (98)
β-lactamase +	6/6 (100)	4/4 (100)	6/6 (100)	16/16 (100)
β-lactamase -	9/9 (100)	17/18 (94)	12/12 (100)	38/39 (97)
<i>M. catarrhalis</i>	13/13 (100)	11/13 (85)	17/17 (100)	41/43 (95)
β-lactamase +	13/13 (100)	10/12 (83)	17/17 (100)	40/42 (95)
β-lactamase -	--	1/1 (100)	--	1/1 (100)
<i>H. parainfluenzae</i>	13/13 (100)	9/10 (90)	6/8 (75)	28/31 (90)
β-lactamase +	2/2 (100)	1/1 (100)	1/1 (100)	4/4 (100)
β-lactamase -	11/11 (100)	8/9 (89)	5/7 (71)	24/27 (89)
<i>S. pneumoniae</i>	14/15 (93)	10/10 (100)	16/16 (100)	40/41 (98)
Penicillin susceptible	11/12 (92)	9/9 (100)	12/12 (100)	32/33 (97)
Penicillin intermediate	3/3 (100)	1/1 (100)	4/4 (100)	8/8 (100)
<i>S. aureus</i>	21/22 (95)	22/23 (96)	23/23 (100)	66/68 (97)
Methicillin resistant	1/1 (100)	--	--	1/1 (100)
Methicillin sensitive	20/21 (95)	22/23 (96)	23/23 (100)	65/67 (97)

<sup>a</sup> A patient may have had more than one pathogen isolated.

**APPEARS THIS WAY  
ON ORIGINAL**

**Table 2.4.a.4. Bacteriologic Eradication Rates for the Major Pathogens,  
Microbiologically Evaluable Patients  
(Study 064 – Excluding Patients Enrolled by Drs. DeAbate and Mathew)**

Pathogen <sup>a</sup>	Number Eradicated/No. Isolated (%)			
	Gatifloxacin 5-Day	Gatifloxacin 7-Day	Clarithromycin 10-Day	Total
Total	50/52 (96)	46/51 (90)	42/44 (95)	138/147 (94)
<i>H. influenzae</i>	12/12 (100)	12/13 (92)	8/8 (100)	32/33 (97)
β-lactamase +	5/5 (100)	4/4 (100)	2/2 (100)	11/11 (100)
β-lactamase -	7/7 (100)	8/9 (89)	6/6 (100)	21/22 (95)
<i>M. catarrhalis</i>	11/11 (100)	8/10 (80)	11/11 (100)	30/32 (94)
β-lactamase +	11/11 (100)	7/9 (78)	11/11 (100)	29/31 (94)
β-lactamase -	--	1/1 (100)	--	1/1 (100)
<i>H. parainfluenzae</i>	5/5 (100)	5/6 (83)	2/4 (50)	12/15 (80)
β-lactamase +	--	1/1 (100)	--	1/1 (100)
β-lactamase -	5/5 (100)	4/5 (80)	2/4 (50)	11/14 (79)
<i>S. pneumoniae</i>	12/13 (92)	5/5 (100)	6/6 (100)	23/24 (96)
Penicillin susceptible	10/11 (91)	4/4 (100)	6/6 (100)	20/21 (95)
Penicillin intermediate	2/2 (100)	1/1 (100)	--	3/3 (100)
<i>S. aureus</i>	9/10 (90)	14/15 (93)	13/13 (100)	36/38 (95)
Methicillin resistant	--	--	--	--
Methicillin sensitive	9/10 (90)	14/15 (93)	13/13 (100)	36/38 (95)

<sup>a</sup> A patient may have had more than one pathogen isolated.

**APPEARS THIS WAY  
ON ORIGINAL**

#### 2.4.b. Study 065

Table 2.4.b.1 summarizes clinical cure rates by prognostic factor for clinically evaluable patients.

**Table 2.4.b.1. Clinical Cure Rates by Prognostic Factor, Clinically Evaluable Patients (Study 065)**

Prognostic Factor/ Subcategory	Number Cured/Evaluable Patients (%)		
	Gatifloxacin N = 127	Azithromycin N = 125	Total N = 252
<u>Exacerbation Type</u>			
Type I	104/127 (82)	92/125 (74)	196/252 (78)
<u>Duration of Current Episode</u>			
0 - 7 Days	57/66 (86)	39/56 (70)	96/122 (79)
> 7 Days	46/57 (81)	49/63 (78)	95/120 (79)
Not Recorded	1/4 (25)	4/6 (67)	5/10 (50)
<u>Systemic or Inhaled Corticosteroid Use at Randomization</u>			
Yes	30/38 (79)	25/35 (71)	55/73 (75)
No	74/89 (83)	67/90 (74)	141/179 (79)
<u>Current Smoking Status</u>			
Smoker	51/62 (82)	48/57 (84)	99/119 (83)
Non-Smoker	53/65 (82)	44/68 (65)	97/133 (73)
<u>History of Smoking</u>			
Yes	81/98 (83)	69/97 (71)	150/195 (77)
No	23/29 (79)	23/28 (82)	46/57 (81)

Table 2.4.b.2 summarizes clinical response at the extended follow-up visit for clinically evaluable patients. Among patients who returned for the follow-up visit, results were similar between treatment groups. More gatifloxacin patients failed to return for the extended follow-up visit (10 gatifloxacin v. 3 azithromycin), however this difference was not significant ( $p=0.13$  using a chi-square test with continuity correction). As outlined in the sponsor's analysis plan, the end of study cure rates are calculated by carrying forward TOC values for those patients with no data at the extended follow-up visit (i.e., cures are carried forward from the TOC visit to the end of study evaluation). If one instead assumes that patients who were lost to follow-up by the end of study are failures, the end of study cure rates are 71% (90/127) for gatifloxacin patients and 67% (84/125) for azithromycin patients.

**Table 2.4.b.2. Clinical Assessment at Extended Follow-up, Clinically Evaluable Patients (Study 065)**

	Numbers of Patients (%)		
	Gatifloxacin N = 127	Azithromycin N = 125	Total N = 252
Cured at Test of Cure Visit	104 (82)	92 (74)	196 (78)
Late Follow-Up Obtained	94 (90)	89 (97)	183 (93)
Sustained Cure	90 (96)	84 (94)	174 (95)
Relapse	4 (4)	5 (6)	9 (5)
Cure Rate at End of Study <sup>a</sup>	100/127 (79)	87/125 (70)	187/252 (74)

<sup>a</sup> 95% Confidence Interval for Difference in Cure Rates (BMS Modification of Fleiss method): (-3.1%, 18.4%)

Table 2.4.b.3 summarizes bacteriologic eradication rates for the major pathogens in all microbiologically evaluable patients.

**Table 2.4.b.3. Bacteriologic Eradication Rates for the Major Pathogens, Microbiologically Evaluable Patients (Study 065)**

Pathogen <sup>a</sup>	Number Eradicated/No. Isolated (%)		
	Gatifloxacin N = 73	Azithromycin N = 74	Total N = 147
Total	77/88 (88)	73/87 (84)	150/175 (86)
<i>H. influenzae</i>	11/12 (92)	15/18 (83)	26/30 (87)
β-lactamase +	2/3 (67)	6/7 (86)	8/10 (80)
β-lactamase -	9/9 (100)	9/11 (82)	18/20 (90)
<i>S. pneumoniae</i>	6/7 (86)	8/9 (89)	14/16 (88)
Penicillin Susceptible	4/5 (80)	8/9 (89)	12/14 (86)
Penicillin Intermediate	2/2 (100)	--	2/2 (100)
<i>M. catarrhalis</i>	24/26 (92)	14/16 (88)	38/42 (90)
β-lactamase +	23/25 (92)	13/15 (87)	36/40 (90)
β-lactamase -	1/1 (100)	1/1 (100)	2/2 (100)
<i>H. parainfluenzae</i>	18/22 (82)	13/18 (72)	31/40 (78)
β-lactamase +	2/2 (100)	--	2/2 (100)
β-lactamase -	16/20 (80)	13/18 (72)	29/38 (76)
<i>S. aureus</i>	16/19 (84)	19/22 (86)	35/41 (85)
Methicillin Resistant	--	1/1 (100)	1/1 (100)
Methicillin Sensitive	16/19 (84)	18/21 (86)	34/40 (85)

<sup>a</sup> A patient may have more than one pathogen isolated pre-treatment.

In terms of the primary efficacy endpoint in this study, clinical response, gatifloxacin appears to perform somewhat more favorably than azithromycin. In clinically evaluable patients, the cure rate for gatifloxacin was 82% while the cure rate for azithromycin was 74% (note that this difference is not significant). However, when examining failures, it appears that gatifloxacin patients who fail might be performing more poorly than azithromycin patients who fail. As a sensitivity analysis, this reviewer performed two analyses where the definition of "cure" was slightly modified. The original definition of cure required, among other things, that all four of the signs and symptoms related to the acute infection (cough, dyspnea, sputum production, and sputum purulence) improve or return to the patient's baseline level. The first sensitivity analysis revised the definition of "cure" to include patients who had at least 3 of the 4 signs and symptoms related to acute infection improve or return to baseline, and who also satisfied the remainder of the original definition of a cure. The second sensitivity analysis included patients as cures who had at least 2 of the 4 signs and symptoms related to acute infection improve or return to baseline, and who again satisfied the remainder of the original definition of cure. Table 2.4.b.4 summarizes results from the first sensitivity analysis, while Table 2.4.b.5 summarizes results from the second sensitivity analysis. In both cases, while the point estimates for cure rates were much closer together, the treatments would still be considered similar using a 15% delta.

**Table 2.4.b.4. First Revised Definition of Cure, Clinically Evaluable Patients (Study 065)  
( $\geq 3$  of 4 Signs/Symptoms Improved or Returned to Baseline)**

Clinical Response	Number of Patients (%)		Total N = 252
	Gatifloxacin N = 127	Azithromycin N = 125	
Cure	106 (83)	106 (85)	212 (84)
Failure	21 (17)	19 (15)	40 (16)

95% Confidence Interval for Difference in Cure Rates (Fleiss method): (-10.5%, 7.5%).

95% Confidence Interval for Difference in Cure Rates (BMS Modification of Fleiss method): (-12.1%, 5.9%).

**Table 2.4.b.5. Second Revised Definition of Cure, Clinically Evaluable Patients (Study 065)  
( $\geq 2$  of 4 Signs/Symptoms Improved or Returned to Baseline)**

Clinical Response	Number of Patients (%)		Total N = 252
	Gatifloxacin N = 127	Azithromycin N = 125	
Cure	107 (84)	109 (87)	216 (86)
Failure	20 (16)	16 (13)	36 (14)

95% Confidence Interval for Difference in Cure Rates (Fleiss method): (-11.5%, 5.7%).

95% Confidence Interval for Difference in Cure Rates (BMS Modification of Fleiss method): (-13.1%, 4.1%).

### 3. Safety

#### 3.1. Study 064

Table 3.1 summarizes clinical adverse event rates by treatment group for all treated patients. Overall adverse event rates were similar when patients enrolled by Drs. DeAbate and Mathew were excluded (35% 5-day gatifloxacin patients, 49% 7-day gatifloxacin patients, and 47% clarithromycin patients). In both populations, 5-day gatifloxacin patients experienced somewhat lower overall adverse event rates.

**Table 3.1. Clinical Adverse Events by Treatment Group, All Treated Patients  
(Study 064 – All Patients)**

Clinical Adverse Events <sup>a</sup>	Number of Patients (%)		
	Gatifloxacin 5-Day N = 174	Gatifloxacin 7-Day N = 175	Clarithromycin 10-Day N = 178
<b><u>Any Clinical Adverse Event</u></b>	60 (34)	76 (43)	76 (43)
Diarrhea	14 (8)	10 (6)	13 (7)
Nausea	9 (5)	12 (7)	10 (6)
Increased coughing	8 (5)	12 (7)	5 (3)
Headache	7 (4)	8 (5)	11 (6)
Dry Mouth	7 (4)	10 (6)	6 (3)
Increased sputum	6 (3)	8 (5)	4 (2)
Dyspnea	6 (3)	8 (5)	5 (3)
Taste perversion	6 (3)	3 (2)	15 (8)
Chest pain	3 (2)	10 (6)	2 (1)
Dizziness	2 (1)	7 (4)	3 (2)
Rhinitis	2 (1)	8 (5)	3 (2)
Vomiting	1 (<1)	5 (3)	1 (<1)

<sup>a</sup> All adverse clinical events occurring in  $\geq 3\%$  of the total number of patients in any of the 3 treatment arms.

There were no deaths reported from the start of dosing up to and including 30 days after the last dose.

Eight (1.5%) treated patients (3 5-day gatifloxacin, 3 7-day gatifloxacin, and 2 clarithromycin patients) experienced 13 serious adverse events, none of which were attributed to study treatment by the investigators. In all cases, the serious adverse events led to hospitalization. The following are brief summaries of the patients' experiences, taken from Section 12.3 of the sponsor's final study report. Note that all but two of these patients (005-029 and 007-039) were considered failures at the TOC visit.

- Five-day gatifloxacin Patient 034-244 was a 48-year-old male who was hospitalized for rectal bleeding (bloody diarrhea) and abdominal pain on Day +3 after completion of gatifloxacin therapy. The patient was admitted on Day +4 to an out-of-state hospital, treated with intravenous

fluids, famotidine and his usual pulmonary agents (including prednisone), and was given ciprofloxacin for chest congestion. During his hospital stay he had one episode of a bloody stool. He was discharged improved after a 4-day stay with the understanding to consult with his primary care physician and a gastroenterologist to further evaluate the causes of his GI bleeding. The patient refused to visit a gastroenterologist despite the advice of his physician to do so. At the time of study closure this patient had not followed up with a gastroenterologist.

- Five-day gatifloxacin Patient 041-346 was a 58-year old female, hospitalized on Day +17 for AECB with impending respiratory failure. She was given cefotaxime intravenously and upon discharge after a 5-day hospitalization was discharged on oral ciprofloxacin. Symptoms were considered resolved, but residual effects of the episode persisted upon discharge.
- Five-day gatifloxacin Patient 051-553 was a 65-year-old female, hospitalized on Day 2 for increased dyspnea due to acute exacerbation of her COPD. She continued on the study medication until Day 5 (the third day of hospitalization) when she was started on ceftriaxone and methylprednisolone, both intravenously. Symptoms resolved after 10 days at which time she was discharged.
- Seven-day gatifloxacin Patient 005-029 was an 82-year-old male who was hospitalized for pneumonia on Day +28. He was treated with unspecified intravenous antibiotics and was released after four days when his condition resolved.
- Seven-day gatifloxacin Patient 007-039 was a 68-year-old male who was re-scheduled for an office visit when blood test results (from blood collected on Day 1) indicated hyperglycemia (433 mg/dL). At that visit (Day 4) the patient was evaluated and prescribed glipizide to control the elevated glucose. On Day 6 the patient went to the ER and was admitted to the hospital for dehydration. His furosemide and theophylline medications were stopped on admission in view of his initial dehydration, and his treatments included hydration and adjustments of glipizide to control glucose levels. He was discharged after four days. During subsequent follow-up the patient was diagnosed as having diabetes mellitus.
- Seven-day gatifloxacin Patient 007-421 was a 73-year-old male who experienced increased dyspnea and elevated temperature on Day +12, and was hospitalized the following day for eight days. His condition was attributed to a viral infection, with similar symptoms observed among fellow residents at his boarding home. His elevated temperature and increased dyspnea resolved after 3 and 8 days, respectively. He was given levofloxacin orally until his discharge.
- Clarithromycin Patient 007-046 was a 77-year-old male who was hospitalized on Day 7 for worsening of COPD, which was attributed to retained secretions. This patient suffered severe respiratory failure, increased fever, and atrial fibrillation that was thought to be pre-existing. Study medications were stopped on Day 7. The patient's treatment consisted of levofloxacin, methylprednisolone, and prednisone; he required intubation and mechanical ventilation. The respiratory failure and fever resolved after 13 days and one day, respectively; the atrial fibrillation was unresolved. The patient was discharged after 13 days.
- Clarithromycin Patient 053-574 was an 82-year-old male, hospitalized on Day +7 for back pain due to a compression fracture of the 7<sup>th</sup> thoracic vertebrae and hypoxia related to COPD. He was treated with acetaminophen with codeine and methylprednisolone. There were no signs of pneumonia or infectious complications but he was given ceftizoxime. When discharged after a four-day hospitalization the hypoxia had resolved.

Ten (2%) treated patients discontinued treatment due to adverse clinical events. The 5-day gatifloxacin, 7-day gatifloxacin, and clarithromycin arms were comparable with respect to the frequency of discontinuations due to adverse events (1%, 2% and 2%, respectively).

Gastrointestinal and central nervous system events were the main reasons leading to discontinuation.

### 3.2. Study 065

Table 3.2 summarizes clinical adverse event rates by treatment group for all treated patients. Gatifloxacin patients experienced slightly higher overall adverse event rates (50% gatifloxacin v. 45% azithromycin).

**Table 3.2. Clinical Adverse Events by Treatment Group, All Treated Patients (Study 065)**

Clinical Adverse Events <sup>a</sup>	Number of Patients (%)	
	Gatifloxacin N = 147	Azithromycin N = 147
<u>Any Clinical Adverse Event</u>	73 (50)	66 (45)
Coughing	12 (8)	8 (5)
Increased Sputum	11 (7)	6 (4)
Rhinitis	11 (7)	8 (5)
Bronchitis	8 (5)	3 (2)
Diarrhea	8 (5)	15 (10)
Dyspnea	8 (5)	7 (5)
Headache	8 (5)	9 (6)
Chest Pain	7 (5)	8 (5)
Nausea	7 (5)	4 (3)
Abdominal Pain	5 (3)	5 (3)
Pharyngitis	5 (3)	6 (4)
Back Pain	4 (3)	2 (1)
Dizziness	4 (3)	4 (3)
Flatulence	4 (3)	0 (0)
Vaginitis	4 (5) <sup>b</sup>	0 (0)
Chills	2 (1)	6 (4)
Pain	2 (1)	5 (3)
Malaise	1 (<1)	7 (5)

<sup>a</sup> All adverse clinical events occurring in  $\geq 3\%$  of the total number of patients in either treatment arm.

<sup>b</sup> Percent based on 82 gatifloxacin-treated females.

There was one death reported during the study period (i.e., from the start of dosing up to and including 30 days after the last dose). The following description is taken from Section 12.2 of the sponsor's final study report. Note that this patient was considered a failure at the TOC visit.

- Patient 051-420 was a seventy-five year-old male with a past medical history of BPH and 'stable leukemia', for which he was not receiving treatment. At the time of his randomization to gatifloxacin on 14 April 2000, his white blood cell count was 52,000, with 15% neutrophils and 82% lymphocytes. His pre-treatment sputum culture was positive for *S. marcescens*. He completed therapy on 18 April and reported improvement in all four cardinal signs and symptoms during the telephone contact on 21 April. When he missed his next scheduled appointment on 27 April, several unsuccessful attempts were made to reach him. On 4 May, the patient's wife phoned the site to inform study staff that the patient had been admitted to the hospital on 27 April with pneumonia, and had died that same day of respiratory failure and cardiac arrest. An autopsy was not performed.

Fourteen (5%) treated patients, seven in each treatment group, experienced 20 serious adverse events, none of which were attributed to study drug. In all cases, the serious adverse events led to hospitalization. The following are brief summaries of the patients' experiences, taken from Section 12.3 of the sponsor's final study report. Note that all but two of these patients (012-231 and 011-173) were considered failures at the TOC visit.

- Patient 002-039 was a 58 year-old female who was hospitalized for worsening bronchitis after three doses of gatifloxacin; in addition, a chest x-ray showed evidence of pneumonia. All events were considered unrelated to study drug. No follow-up information was available, but the study site indicated on a later query that the events had resolved.
- Patient 011-174 was a 31 year-old female who was hospitalized with worsening bronchitis symptoms five days after completing a course of gatifloxacin; all events were considered unrelated to study drug, and resolved three days later.
- Patient 012-231 was a 42 year-old female who completed five days of gatifloxacin therapy and was hospitalized with severe lower back pain on Day +18. She underwent lumbar laminectomy and discectomy on Day +21 and was discharged two days later. This event was considered unrelated to study drug.
- Patient 018-198 was a 53 year-old white male who was hospitalized with worsening symptoms of COPD exacerbation on the last day of gatifloxacin therapy; this event was considered unrelated to study drug. He was treated with levofloxacin and clindamycin and discharged eleven days later.
- A 47 year-old female (045-261) was hospitalized for evaluation and management of dysfunctional uterine bleeding and chronic pelvic pain some time after completing five days of gatifloxacin therapy. She underwent abdominal hysterectomy on Day +30 and was discharged five days later. The events were considered unrelated to study drug.
- A 44 year-old male (045-266) was hospitalized for severe bronchitis/flu syndrome two days after starting gatifloxacin therapy; these events were considered unrelated to study drug. Minimal follow-up information was available but the study site indicated that the acute nature of the events resolved but there were residual symptoms as of April 2000.
- Patient 051-420 was a 75 year-old white male who completed a five day course of gatifloxacin; at the time of the post-treatment telephone contact, he reported an improvement in his symptoms. The patient did not return for subsequent office visits, however, and the site learned that he had been hospitalized for pneumonia on Day +9 and died. These events were considered unrelated to study drug.

- Patient 010-189 was a 43 year-old female who was hospitalized for pneumonia after receiving only one dose of azithromycin; she was discharged five days later. This event was judged to be unrelated to study drug.
- A 49 year-old female (010-193) was hospitalized for worsening symptoms of exacerbation after receiving only one dose of azithromycin; she was discharged three days later. The event was considered unrelated to study drug.
- Patient 011-173 was a 39 year-old schizophrenic male who, fifteen days after completing a course of azithromycin, was hospitalized for alcohol detoxification. This event was considered unrelated to study drug. The patient was discharged eight days later.
- An 81 year-old male (018-058) was hospitalized with symptoms of a COPD exacerbation twenty-two days after completing five days of azithromycin; he was discharged after an eight day stay. The event was considered unrelated to study drug.
- Patient 018-320 was a 45 year-old white male who completed a course of azithromycin and was subsequently hospitalized twice within three weeks. The first hospitalization, on Day +9, was for an asthma exacerbation; the second, on Day +30, was for an asthma exacerbation and chronic bronchitis. Both hospitalizations were brief (two and three days, respectively). All events were considered unrelated to study drug.
- A 70 year-old male (030-235) was hospitalized with cholelithiasis seventeen days after completing a course of azithromycin. A laparoscopic cholecystectomy was attempted; because of significant inflammation, an open cholecystectomy was performed. The patient was discharged after 3 days later. The event was considered unrelated to study drug.
- Patient 041-137, a 63 year-old male, was hospitalized for the evaluation of chest pain; he had completed a course of azithromycin four days previously. His symptoms were attributed to gastroesophageal reflux, and he was discharged three days later. The event was judged unrelated to study drug.

Six (2%) treated patients, 2 gatifloxacin and 4 azithromycin patients, discontinued treatment due to adverse clinical events. One gatifloxacin patient experienced chest pain, dry mouth, dyspnea, and confusion; while the other gatifloxacin patient experienced bronchitis and flu syndrome. Of the azithromycin patients: one experienced abdominal pain; a second, pneumonia; a third, diarrhea and an enlarged abdomen; and a fourth, nausea, nervousness, tachycardia, and vomiting.

**APPEARS THIS WAY  
ON ORIGINAL**

### **III. CONCLUSIONS**

Gatifloxacin (Tequin) is currently approved for the treatment of AECB. The approved treatment regimen is 400mg (oral or intravenous) given once daily for 7-10 days. In this supplemental New Drug Application, the sponsor has submitted two controlled clinical trials, studies 064 and 065, to support reducing the duration of treatment for AECB to 5 days. Study 064 compares a 5-day course of oral gatifloxacin, given 400mg QD, to both a 7-day course of oral gatifloxacin given 400mg QD and a 10-day course of oral clarithromycin given 500mg BID. The primary comparison in study 064 was between the 5-day gatifloxacin and clarithromycin regimens. Study 065 compares a 5-day course of oral gatifloxacin given 400mg QD to a standard regimen of azithromycin (500 mg PO on day 1, followed by 250 mg PO on days 2-5). The primary efficacy endpoint in each study was the clinical cure rate at the test-of-cure visit, 5 to 18 days post-therapy. The sponsor considered the results in the clinically evaluable patient population to be primary. This reviewer considers the results in eligible patients to be equally important.

In both studies, efficacy rates were found to be similar among treatment groups. In study 064, the 95% confidence interval for the difference in clinical cure rates, 5-day gatifloxacin minus clarithromycin, was (-6.1%, 7.0%) in all clinically evaluable patients, and (-5.3%, 12.3%) in clinically evaluable patients excluding those enrolled by Drs. DeAbate and Mathew. In eligible patients in study 064, the 95% confidence intervals for the difference in clinical cure rates, 5-day gatifloxacin minus clarithromycin, were (-7.7%, 6.4%) (all eligible patients), and (-6.3%, 11.6%) (eligible patients excluding those enrolled by Drs. DeAbate and Mathew). In study 065, the 95% confidence interval for the difference in cure rates, gatifloxacin minus azithromycin, was (-3.4%, 17.0%) in clinically evaluable patients and (-5.2%, 15.3%) in eligible patients.

Safety results appear to be similar between treatment arms in both studies. In study 064, gatifloxacin patients experienced somewhat lower overall adverse event rates (all treated patients: 34% 5-day gatifloxacin patients, 43% 7-day gatifloxacin patients, and 43% clarithromycin patients; all treated patients excluding those enrolled by Drs. DeAbate and Mathew: 35% 5-day gatifloxacin patients, 49% 7-day gatifloxacin patients, and 47% clarithromycin patients). In study 065, gatifloxacin patients experienced slightly higher overall adverse event rates (50% gatifloxacin v. 45% azithromycin).

#### **RECOMMENDED REGULATORY ACTION:**

**From a statistical perspective, the data provided by the sponsor in this submission support the approval of a 5-day course of treatment, 400mg gatifloxacin QD, in the treatment of acute exacerbations of chronic bronchitis.**

151

Nancy Silliman, Ph.D.  
Statistical Reviewer  
Special Government Employee (SGE)

Concur: Karen Higgins, Sc.D.  
Statistical Team Leader, DB III

cc:

Orig. NDA #21-061 SE2-007

Orig. NDA #21-062 SE2-008

HFD-590

HFD-590/Dr. Goldberger

HFD-590/Dr. Roca

HFD-590/Dr. Johann-Liang

HFD-590/Ms. Willard

HFD-725/Dr. Huque

HFD-725/Dr. Higgins

HFD-700/Dr. Anello

HFD-590/Dr. Cavaille-Coll

This review contains 24 pages.

**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**

---

/s/

-----  
Karen Higgins  
9/13/01 11:33:37 AM  
BIOMETRICS  
Signing for Nancy Silliman

Karen Higgins  
9/13/01 11:36:07 AM  
BIOMETRICS